

respectfully traversed. Applicants' postcard submitted with the application lists the inclusion of an Abstract, as the appended copy thereof shows.

In addition, the retained file copy in the possession of applicant's attorney includes an abstract on a separate sheet and a copy thereof is appended.

C. Claim Rejections--35 U.S.C. § 112

The rejection of Claims 1-9 as not based upon an enabling disclosure is not understood. This application incorporates by reference the entire disclosure of commonly assigned application Serial No. 09/139,720 as the rejection acknowledges. M.P.E.P. § 2163.07 states that

"Instead of repeating some information contained in another document, an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. The information incorporated is as much a part of the application as filed as if the text were repeated in the application, and should be treated as part of the text of the application as filed."

Application Serial No. 09/139,720 teaches in detail the preparation of antibodies specific to O-carbohydrate antigens of Legionella, including Legionella pneumophila and contains examples that describe preparing antibodies specific to a particular O-carbohydrate antigen of Legionella pneumophila, i.e., to the O-polysaccharide antigen of Legionella pneumophila serogroup I. This application incorporates all of that disclosure by reference and further describes marked improvements in sensitivity and specificity of assays for Legionella pneumophila in environmental water samples (including assays for Legionella pneumophila serogroup I in such samples), that are achieved by substituting for polyclonal antibodies to Legionella pneumophila, the antigen-specific antibodies to O-carbohydrate antigens (obtained by procedures described in detail in the incorporated-by-reference application, Serial No.

09/139,720) in known enzyme immunoassay procedures. In other words, the incorporated-by-reference application describes the procedure for obtaining highly antigen-specific antibodies to Legionella O-carbohydrate antigens, especially Legionella pneumophila O-carbohydrate antigens. This application describes and claims how known enzyme immunoassays for detecting Legionella pneumophila in environmental water samples are improved in sensitivity and specificity so as to provide informative results adequate to effective environmental monitoring, within a period of time that enables effective abatement of environmental sources of Legionella pneumophila, e.g., in cooling tower water, in stagnant water pools and other such places within a rapid turn-around time. The inadequacies of methodologies heretofore used to detect Legionella pneumophila serogroup I in environmental water samples--i.e. bacterial culture, direct fluorescence assays and polymeric chain reaction ("PCR") assays are set forth at pages 1-3 of the specification.

The Office Action strongly suggests that the Examiner is ignoring the practical difficulties of arriving at a relatively rapid, highly specific and sensitive test for Legionella pneumophila in environmental water, and the fact that Applicants have overcome them by the use of an EIA assay that employs the purified antigen-specific antibodies to Legionella pneumophila O-carbohydrate antigens that are fully described in the incorporated-by-reference application Serial No. 09/139,720.

If the Examiner means to suggest, by the final sentence of paragraph 3 of the Office Action that physical inclusion of incorporated--by-reference material in this application should be made, then it is requested that a clear and unmistakable indication to that effect be supplied. The identified sentence of the Action is simply not understood.

Furthermore, the first unnumbered paragraph on p.2 of the action is completely

unclear. There is no doubt that, in testing environmental water samples for Legionella pneumophila serogroup 1, purified antigen-specific antibodies which are specific to its O-polysaccharide antigen are contemplated to be utilized by substituting them for raw antibodies in known EIA procedures. If environmental water samples are to be tested for other serogroups of Legionella pneumophila, as is also contemplated even though not presently considered as important as testing for serogroup I, then the antibodies to be utilized in the EIA are antibodies specific to the corresponding O-carbohydrate antigens(s) of the serogroup(s) to be tested for.

Just what the Examiner has in mind in the final two sentences of this unnumbered paragraph is particularly unclear. The testing of environmental water samples is directed toward ascertaining whether certain Legionella bacteria known to contain O-carbohydrate antigens are present. Testing as described in this application does that relatively rapidly and highly effectively. But O-carbohydrate antigens, including the O-polysaccharide antigen of L. pneumophila serogroup 1 are necessary components of L. pneumophila bacteria and do not have to be "made" as these sentences appear to suggest.

Numbered paragraph 4 of the action is likewise not understood. It rejects claims 1-9 as indefinite for failing to particularly point out and distinctly claim what applicants regard as their invention and then goes on to say that "the steps in claims are directed to making antibodies" and "there are no method steps to detect Legionella". None of this is understood. What applicants regard as their invention is using the purified antigen specific antibodies to L. pneumophila which are obtained according to the incorporated-by-reference material, in any known enzyme immunoassay procedure and conducting it on environmental water samples. Applicants are not inventors of any specific technique for performing an enzyme immunoassay;

they are inventors of a satisfactory, relatively rapid, highly sensitive and highly specific assay for Legionella pneumophila in environmental water samples which is especially desirable to human safety because it allows rapid treatment of the water supply from which the samples came, so as to make it safe to humans. The specification teaches at length that any known enzyme immunoassay protocol for contacting water samples with the purified antigen specific antibodies may be used, any enzyme label can be used, any type of detection step for enzyme immunoassay can be used and any method of correlating detection of L. pneumophila O-carbohydrate antigen to the presence of L. pneumophila may be used.

Moreover, none of the claims defines an antibody purification step, with the possible-exception of Claim 1. It is not understood how the Examiner arrived at this misconception. More pointedly,

(a). Claim 1 mentions how the antibodies were purified only for the purpose of identifying the antibodies.

(b). Claims 2, 3 and 4 are concerned solely with preliminary concentration of environmental water samples to segregate all of the Legionella bacteria contained in a relatively large water sample (e.g. at least 100 ml.) into a tiny volume that is feasible and practical to assay by EIA.

(c). Claims 5 defines the conditions of an enzymeimmunoassay test which is the subject of specific examples in the specification. Today applicants' assignee markets test kits for environmental water testing which comprise tubes precoated with the purified antigen-specific antibodies, further unbound purified antigen specific antibodies in a suitable container horseradish peroxidase for labelling in a suitable container and directions for conducting an enzyme-labelled sandwich immunoassay on environmental water therewith. This claim covers this specific assay.

(d). Claim 6 defines a preferred range of amounts of the purified antigen specific antibodies to be used in the test, e.g. by coating on coated tubes and/or a coated solid insert, in order to obtain the sensitivity described in the specification.

Claim 7 defines the lower limit of solid surface bound antibody per test in order to achieve the stated sensitivity.

(e). Claim 8 covers EIA detection of Legionella pneumophila serotypes in water

samples other than serotype 1, using purified antibodies specific to the O-carbohydrate antigen of each such serotype.

(f). Claim 9 covers EIA detection of other Legionella species in water samples using purified antibodies to their O-carbohydrate antigens.

Paragraph 5 of the Office Action (p. 3) suggests either that there is some mystery about how enzyme labels are attached to antibodies or that the labelling method is part of Applicants' invention Applicants' specification makes it clear that any enzyme label may be conjugated or otherwise attached to the antibodies by any method that works.

Paragraphs 6 and 7 have been obviated by the amendments to Claim 1 made herein.

D. Claim Rejections--35 U.S.C. § 103

None of the references cited in the Office Action addresses the problem solved by the present invention, which is that of providing a rapid and accurate assay for detecting 1,000 and smaller amounts of colony forming units of Legionella bacteria per milliliter in environmental water samples, which assay can effectively be used to monitor water in cooling towers of buildings, etc. to insure that danger of infecting humans who are exposed to that water is kept to a specified minimum safe level and to further insure that the water is treated to kill these bacteria if the specified minimum safe level is exceeded.

The Office Action presents a speculative discussion that in no way addresses the invention disclosed or any facet of its patentability.

First of all, Applicants do not claim to have invented the use of spacer molecules in affinity chromatography to separate a ligand or other product to be purified from a matrix backbone--and Cuatrecasas *et al* is hence irrelevant. Nor do they claim to have invented the

magnetic microspheres disclosed by Yen *et al* or the uses thereof that Yen *et al* disclose.

Secondly, the present invention has nothing to do with the monoclonal antibodies disclosed by Strosberg *et al* or Barthe *et al*. To date, it has not been shown that any monoclonal antibody, including that disclosed by Barthe *et al* and those disclosed by Strosberg *et al*, is highly useful in detecting Legionella bacteria, including L. pneumophila serogroup 1. Neither reference even shows what antigen of Legionella its monoclonal antibody binds to or otherwise demonstrates any relevance to the invention described in the present application, Moreover, even if arguendo, a monoclonal antibody of the prior art could be shown to be capable of yielding comparable results in comparable assays of environmental water samples to the purified antigen-specific antibodies utilized by Applicants this would not deprive Applicants' invention of patentability under either 35 U.S.C. §§ 102 or 103. It is axiomatic that multiple ways of arriving at a given result may each be patentable.

The Examiner, moreover, is completely wrong in postulating the "No more than routine skill in [sic is] involved in adjusting the amount of a component such as water or antibody...to achieve the results taught in the prior art. This overgeneralization suggests, inter alia that adjusting the amount of polyclonal antibodies to *L. pneumophila* serogroup I could produce the result disclosed and claimed in the present application; careful attention to the teaching of Applicants' specification, however, shows this to be a canard. In addition, the requirements of relative rapidity and very high sensitivity that are essential to environmental testing of potentially dangerous water samples cannot be satisfied by mere "balancing" such as the Examiner postulates. Nor are these requirements even marginally met by rampant speculation from Strosberg *et al* about how the therein disclosed monoclonal antibodies--which have achieved no recognition whatever in the real world of actual testing --might be used.

The Imrich *et al* reference is directed primarily to a device, the only actual use of which shown therein is in detecting Group A streptococcus. The speculation concerning its possible use to detect Legionella pneumophila has led to nothing in the least confirmatory in the eight years since the filing of the underlying application. Imrich *et al* conveniently categorized antibodies under a broad brush "immunoglobulin" category which is a dead giveaway that no antibody to any bacterium but Group A Streptococcus was ever specifically worked with and that all that is said about other bacteria is at best unexplored theorization.

The Office Action fails to make any analogy whatsoever between Jurgens and the present invention. Jurgens is concerned with raw antibodies (see "Preparation of antisera", p. 2181) having no antigen specificity and the results have no clear relationship to any work by Applicants.

Of the numerous permutations and combinations of Imrich *et al*, Strosberg *et al*, Barthe *et al*, Jurgens, Cuatrecasas *et al* and Yen *et al* postulated in the action, none of them renders the Applicants' invention as claimed--if properly understood--even remotely obvious to one of ordinary skill in the art. Moreover, the elaborate maneuvering required even to postulate a reason for combining these references totally exposes the lack of merit in each postulated combination and its failure to show any claim to which it has been applied to be obvious under 35 U.S.C. § 103. The Examiner is reminded that the Court of Appeals for the Federal Circuit increasingly continues to render decisions that hold, in substance, that a valid combination of references under 35 U.S.C. § 103 must rest on some suggestion contained in one or more of the references that the combination should be made. These references, singly and together, lack even a scintilla of such a suggestion.

The action refers to prior art made of record and not relied upon, but there is no

identification of any of Ciesielski *et al*, Kazandijian *et al* or Kohler *et al* on the "Notice of References Cited" received by Applicants.

CONCLUSION

The Office Action is baffling and appears unrelated in many respects to the specific problem addressed by Applicants.

Other parts of the Action are not understood at all.

Given the apparent remoteness of the references to Applicants' disclosure, Applicants can only conclude that their claims are in condition for allowance. Early action to that effect is accordingly sought.

Respectfully submitted,



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Enclosed:

UTILITY PATENT APPLICATION TRANSMITTAL; FEE TRANSMITTAL (in duplicate); ABSTRACT; VERIFIED STATEMENT OF SMALL ENTITY STATUS; PATENT APPLICATION; DRAWING PAGE; CHECK IN THE AMOUNT OF \$380.00

Serial No.: APPLIED FOR

Filing Date: DECEMBER 10, 1999

Title: EIA FOR MONITORING
LEGIONELLA PNEUMOPHILA
PRESENCE IN WATER
SAMPLES

Inventors: Norman James Moore
Myron Whipkey
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Please return this card to
the address indicated on reverse.



ABSTRACT OF THE DISCLOSURE

A qualitative and quantitative EIA for detecting *L. pneumophila* in water samples is disclosed. Critical to the disclosed levels of sensitivity of these EIA's is the use of antigen-specific antibodies to the target *L. pneumophila* antigen that have been rendered antigen-specific by affinity purification on a chromatographic column, which antibodies and their purification are described in detail in parent application Serial No. 09/139,720 filed August 25, 1998.